NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

2-BUTOXYETHANOL

(CAS NO. 111-76-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

March 2000

NTP TR 484

NIH Publication No. 00-3974

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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CONTENTS

ABSTRACT

CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-OH

2-BUTOXYETHANOL

CAS No. 111-76-2

Chemical Formula: $C_6H_{14}O_2$ Molecular Weight: 118.17

Synonyms: 2-Butoxy-1-ethanol; *m*-butyl ether; butyl glycol; ethylene glycol monobutyl ether
Trade name: Butyl Cellosolve

2-Butoxyethanol is a member of a family of ethylene glycol monoalkyl ethers. It is used extensively as a solvent in surface coatings such as lacquers, enamels, varnishes, and latex paint; in paint thinners, paint stripping formulations, and inks; and in degreasers and industrial and household cleaners. 2-Butoxyethanol was nominated for study because of its widespread use in industrial and consumer applications, the potential for exposure to workers and the general population, and the absence of chronic toxicity data. Male and female F344/N rats and B6C3F_1 mice were exposed to 2-butoxyethanol (greater than 99% pure) by inhalation (primary route of human exposure) for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and the bone marrow of male F344/N rats and B6C3F_1 mice.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm, 6 hours per day, 5 days per week for 14 weeks. One female rat in the 250 ppm group was killed moribund during week 8; four females in the 500 ppm group were killed moribund during week 1 and one during week 5. Final mean body weights of females exposed to 500 ppm were significantly less than those of the chamber controls. Clinical findings included abnormal breathing, pallor, red urine stains, nasal and eye discharge, lethargy, and increased salivation and/or lacrimation. Due to vascular thrombosis and infarction in the tail vertebrae of 500 ppm female rats, the tails became necrotic and either sloughed off or were chewed off. The primary effect on the hematopoietic system was an anemia characterized as macrocytic, normochromic, and regenerative in males exposed to 125 ppm or greater and, to a greater extent, in all exposed groups of females. Compared to the chamber controls, kidney weights of males exposed to 500 ppm and females exposed to 125 ppm or greater and liver weights of males exposed to 250 or 500 ppm and females exposed to 125 ppm or greater were significantly increased, and thymus weights of females exposed to 500 ppm were significantly less. In female rats killed moribund, there was considerable histologic evidence of thrombosis in tissues and organs including the nasal cavity, incisors, liver, lung, and heart. In addition to thrombosis, infarction occurred in the vertebrae of the tail resulting in necrosis and loss of the distal portion of the tail. There were also inflammation, necrosis, and ulceration of the forestomach; necrosis and centrilobular degeneration of the liver; renal tubule

degeneration; and atrophy of the spleen and thymus. Exposure-related increases in the incidences of Kupffer cell pigmentation, forestomach inflammation and epithelial hyperplasia, bone marrow hyperplasia, splenic hematopoietic cell proliferation, and renal tubule pigmentation were observed in male and/or female rats surviving to the end of the study.

14-Week Study in Mice

Groups of 10 male and 10 female mice were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm, 6 hours per day, 5 days per week for 14 weeks. Two male and two female mice exposed to 500 ppm died and two males and two females were killed moribund during the first 2 weeks of the study. Final mean body weights of 125, 250, and 500 ppm male mice were significantly less than those of the chamber controls. Clinical findings were observed only in 500 ppm males and females that died or were killed moribund and included abnormal breathing, red urine stains, and lethargy. Hematologic evaluation indicated an anemia that was characterized as normocytic, normochromic, and regenerative in mice exposed to 62.5 ppm or greater; the anemia was more pronounced in females. Liver weights of males exposed to 500 ppm were significantly greater than the chamber controls. In mice either dying early or killed moribund, there were inflammation, necrosis, and ulceration of the forestomach; mediastinal pleura and peritoneal inflammation associated with the forestomach lesions; liver necrosis; renal tubule degeneration; atrophy of the spleen, thymus, and mandibular and mesenteric lymph nodes; and degeneration of the testis. Exposure-related increases in the incidences of hematopoietic cell proliferation and hemosiderin pigmentation of the spleen, Kupffer cell hemosiderin pigmentation of the liver, inflammation and epithelial hyperplasia of the forestomach, and renal tubule hemosiderin pigmentation occurred in male and/or female mice surviving to the end of the study.

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 31.2, 62.5, or 125 ppm, 6 hours per day, 5 days per week for 104 weeks. For hematology and bone marrow analyses, additional groups of 27 male and 27 female rats were exposed to 0, 62.5, or 125 ppm for evaluation at 3, 6, and 12 months and nine male and nine female rats were exposed to 31.2 ppm for evaluation at 3 (hematology only) and 6 months.

Survival and Body Weights

Survival of exposed male and female rats was similar to the chamber control groups. The mean body weights of females exposed to 125 ppm were generally less than the chamber control group.

Hematology and Bone Marrow Cellularity

The most consistent exposure-related effect on the hematopoietic system was an exposure concentration-related mild macrocytic, normochromic, regenerative anemia present at 3, 6, and 12 months, with females more affected than males. Significant increases in bone marrow cellularity and decreases in the myeloid/erythroid ratio relative to the chamber controls were observed at all time points in females exposed to 125 ppm, and a decrease in the myeloid/erythroid ratio was observed in males exposed to 125 ppm at 12 months.

Pathology Findings

The incidence of benign or malignant pheochromocytoma (combined) of the adrenal medulla in females exposed to 125 ppm was not significantly increased compared to the chamber controls but exceeded the historical control range. Exposure-related increases in the incidences of hyaline degeneration of the olfactory epithelium and Kupffer cell pigmentation of the liver were observed in male and female rats.

2-Year Study in Mice

Groups of 50 male and 50 female mice were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 62.5, 125, or 250 ppm, 6 hours per day, 5 days per week for 104 weeks. For hematology and bone marrow analyses, additional groups of 30 male and 30 female mice were exposed to 0, 62.5, 125, or 250 ppm for evaluation at 3, 6, and 12 months.

Survival and Body Weights

Survival of male mice exposed to 125 or 250 ppm was significantly less than that of the chamber control group. The mean body weights of exposed males

were generally less than those of the chamber control group during the last 6 months of the study. The mean body weights of exposed female mice were less than those of the chamber control group; the reductions were greater and occurred earlier than those observed in males.

Hematology

The most consistent exposure-related effect on the hematopoietic system was an exposure concentration-related minimal normocytic, normochromic, regenerative anemia present at 3, 6, and 12 months, with females affected slightly more than males.

Pathology Findings

In females exposed to 250 ppm, incidences of forestomach squamous cell papilloma and squamous cell papilloma or carcinoma (combined) were significantly increased relative to the chamber controls, and these incidences exceeded the ranges in historical chamber controls. In 2-butoxyethanol exposed males, there were possible exposure-related increases in the incidences of squamous cell papilloma of the forestomach, although the increases were not significant and the incidences were within the historical control range for chamber controls. Accompanying these neoplasms in females and, to a lesser extent, in males were exposure-related increases in the incidences of ulcer and epithelial hyperplasia of the forestomach.

In male mice exposed to 250 ppm, the incidence of hemangiosarcoma of the liver was significantly increased relative to chamber controls and exceeded the range in historical controls; in addition, there were possible exposure-related increases in the incidence of hepatocellular carcinoma. Incidences of hemosiderin pigmentation in the Kupffer cells were significantly increased in 125 and 250 ppm males and all exposed groups of females.

The incidences of splenic hematopoietic cell proliferation and hemosiderin pigmentation were generally increased in males and females, and the incidences of bone marrow hyperplasia were increased in males. The incidences of hyaline degeneration of the olfactory and respiratory epithelia of the nose were increased in female mice.

GENETIC TOXICOLOGY

2-Butoxyethanol did not induce mutations in any of the *S. typhimurium* strains tested, with or without induced hamster or rat liver S9. 2-Butoxyethanol induced cycle delay but did not induce either sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells with or without S9. 2-Butoxyethanol did not induce micronuclei in bone marrow cells of male rats or mice administered the chemical by intraperitoneal injection three times at 24-hour intervals.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of 2-butoxyethanol in male F344/N rats exposed to 31.2, 62.5, or 125 ppm. There was *equivocal evidence of carcinogenic activity* of 2-butoxyethanol in female F344/N rats based on the increased combined incidences of benign or malignant pheochromocytoma (mainly benign) of the adrenal medulla. There was *some evidence of carcinogenic activity* of 2-butoxyethanol in male B6C3F_1 mice based on increased incidences of hemangiosarcoma of the liver. A marginal increase in the incidences of forestomach squamous cell papilloma and an increase in the incidences of hepatocellular carcinoma may have been exposure related. There was *some evidence of carcinogenic activity* of 2-butoxyethanol in female B6C3F_1 mice based on increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma).

Increased incidences of forestomach neoplasms in male and female mice occurred in groups in which ulceration and hyperplasia were also present.

Exposure to 2-butoxyethanol caused a mild regenerative anemia and effects secondary to the anemia.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2-Butoxyethanol

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 31.2, 62.5, and 125 ppm	Chamber control, 31.2, 62.5, and 125 ppm	Chamber control, 62.5, 125, and 250 ppm	Chamber control, 62.5, 125, and 250 ppm
Body weights	Exposed groups similar to the chamber control group	125 ppm group less than the chamber control group	Exposed groups generally less than the chamber control group	Exposed groups less than the chamber control group
Survival rates	19/50, 11/50, 21/50, 24/50	29/50, 27/50, 23/50, 21/50	39/50, 39/50, 27/50, 26/50	29/50, 31/50, 33/50, 36/50
Nonneoplastic effects	Nose: olfactory epithelium, hyaline degeneration (13/48, 21/49, 23/49, 40/50) Liver: Kupffer cell pigmentation (23/50, 30/50, 34/50, 42/50)	Nose: olfactory epithelium, hyaline degeneration (13/50, 18/48, 28/50, 40/49) Liver: Kupffer cell pigmentation (15/50, 19/50, 36/50, 47/50)	Forestomach: ulcer (1/50, 2/50, 9/49, 3/48); epithelium hyperplasia (1/50, 7/50, 16/49, 21/48) Liver: Kupffer cell pigmentation (0/50, 0/50, 8/49, 30/49) Spleen: hematopoietic cell proliferation (12/50, 11/50, 26/48, 42/49); hemosiderin pigmentation (0/50, 6/50, 45/48, 44/49) Bone Marrow: hyperplasia (0/50, 1/50, 9/49, 5/50)	Forestomach: ulcer (1/50, 7/50, 13/49, 22/50); epithelium hyperplasia (6/50, 27/50, 42/49, 44/50) Liver: Kupffer cell pigmentation (0/50, 5/50, 25/49, 44/50) Spleen: hematopoietic cell proliferation (24/50, 29/50, 32/49, 35/50); hemosiderin pigmentation (39/50, 44/50, 46/49, 48/50) Nose: olfactory epithelium, hyaline degeneration (6/50, 14/50, 11/49, 12/50); respiratory epithelium, hyaline degeneration (17/50, 35/50, 26/49, 23/50)
Neoplastic effects	None	None	Liver: hemangiosarcoma (0/50, 1/50, 2/49, 4/49)	Forestomach: squamous cell papilloma (0/50, 1/50, 2/50, 5/50); squamous cell papilloma or carcinoma (0/50, 1/50, 2/50, 6/50)
Uncertain findings	None	Adrenal Medulla: benign or malignant pheochromocytoma (3/50, 4/50, 1/49, 8/49)	Forestomach: squamous cell papilloma (1/50, 1/50, 2/49, 2/49) Liver: hepatocellular carcinoma (10/50, 11/50, 16/49, 21/49)	None
Level of evidence of carcinogenic activity	No evidence	Equivocal evidence	Some evidence	Some evidence

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2-Butoxyethanol

Genetic toxicology	
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, TA1535, and TA1537, with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Micronucleated erythrocytes	
Rat bone marrow *in vivo*:	Negative
Mouse bone marrow *in vivo*:	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on 2-butoxyethanol on 30 October 1998 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 30 October 1998 the draft Technical Report on the toxicology and carcinogenesis studies of 2-butoxyethanol received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.H. Roycroft, NIEHS, introduced the toxicology and carcinogenesis studies of 2-butoxyethanol by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on the survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. In addition to the standard core study, a number of animals were assessed for hematologic parameters and bone marrow cellularity and myeloid/erythroid ratios. Additionally, animals were included in the design for toxicokinetic measures of 2-butoxyethanol and its principal metabolite, 2-butoxyacetic acid. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male F344/N rats, *equivocal evidence of carcinogenic activity* in female F344/N rats, and *some evidence of carcinogenic activity* in male and female B3C6F$_1$ mice.

Dr. Medinsky, a principal reviewer, agreed in principle with the proposed conclusions. Her concern was that the proposed conclusions for female rats and male mice were made based on differences in response of the test animals compared with historical control values and were not based on differences in response compared to respective controls. She asked what objective statistical measure of differences was used. Dr. Roycroft responded that, as a rule, neoplasm data are not compared statistically with historical control data because so many factors can vary from study to study. The concurrent controls are still considered the most appropriate control group. Dr. J.K. Haseman, NIEHS, said that many factors, such as whether there were increases in incidences of preneoplastic lesions, factored into a decision. Dr. Medinsky commented that one of the report's strengths was the comprehensive section on the chemical disposition and toxicokinetics of 2-butoxyethanol and 2-butoxyacetic acid and suggested a summary paragraph for the chemical disposition and toxicokinetics data (pages 19-20).

Dr. Bailer, the second principal reviewer, agreed with the proposed conclusions for rats but not for mice. He thought that not enough consideration was given to the strong exposure-related trends in the neoplasm data in mice. He asked for clarification as to why the findings did not support a conclusion of *clear evidence* in mice. Dr. Roycroft said that benign and malignant neoplasms are analyzed independently and in combination, with the most important being the combined neoplasms. For male mice, the combined incidences of hepatocellular adenoma or carcinoma did not increase, and the incidences of carcinoma alone were within the historical control range. Dr. J.R. Hailey, NIEHS, noted that whether more emphasis is given to the combined neoplasm incidence depends somewhat on the neoplasm type. With liver neoplasms, there is a morphologic and biologic continuum of progression from foci to adenomas and to carcinomas. Further, it is often difficult to distinguish benign from malignant neoplasms.

Dr. Cullen, the third principal reviewer, agreed with the proposed conclusions. He said that, in the liver of male mice, reliance on historical control incidence and lack of concordant increases in preneoplastic and benign lesions supported less than *clear evidence*, but the data appeared to reflect at least *equivocal evidence*. In female mice, he found the proposed conclusion regarding squamous papillomas appropriate. Dr. Cullen commented that some of the toxic effects attributed directly to action of the chemical might be addressed as secondary responses due to other insults created by the chemical, e.g., anemia in response to blood loss from gastric ulceration in female, and perhaps male, mice.

Dr. T.R. Tyler, Chemical Manufacturers Association Ethylene Glycol Ethers Panel, stated that 2-butoxyethanol has long been recognized primarily as a hemolytic agent, with humans being less susceptible than rodents. Regarding the forestomach neoplasms in female mice, he thought that *some*

evidence was probably correct but likely irrelevant because there is no such organ in humans. Regarding the pheochromocytomas in female rats, he asked the Subcommittee to reconsider the designation of *equivocal evidence* as there were no statistically significant pairwise comparisons, the incidence was barelyoutside the historical control range, and there was no indication of increased incidences in males.

Dr. R. Boatman, Eastman Chemical Company, thought that hemangiosarcomas of the liver in male mice represented a marginal or equivocal finding. He compared the results for this study with those from the NTP bioassay of *p*-nitroaniline (NTP, 1993a), for which similar incidences of hemangiosarcomas of the liver in male mice were classified as equivocal evidence. Further, he stated that the possibility that the study was compromised by *Helicobacter* infection could not be ruled out. Dr. Medinsky asked for staff comment on the *p*-nitroaniline study. Dr. Roycroft responded that the *p*-nitroaniline study was a gavage study and that the historical control range and high incidence for gavage studies at the time were slightly higher than the range and high incidence for the current inhalation study of 2-butoxyethanol.

Dr. Medinsky moved that under the conditions of this study, the Technical Report on 2-butoxyethanol be accepted with revisions discussed and the conclusions as written. Dr. Bailer seconded the motion. Dr. Cullen asked whether a sentence could be added to the conclusion for male mice that there was an exposure-concentration related increase in the incidences of malignant hepatocellular neoplasms. Dr. Roycroft noted that the increased incidences of hepatocellular neoplasms in male mice could be added to the sentence about the marginal increases in the incidences of forestomach neoplasms. There was consensus that that addition would be acceptable. The motion was accepted with five yes votes with one abstention (Dr. Bus).